neuron to another. Transcriptional dysregulation has been implicated in HD, based on the observation that mutant forms of huntingtin bind various transcriptional regulators. Some of the transcription factors that are sequestered by mutant huntingtin include those involved in mitochondrial biogenesis and protection against oxidative injury, and their reduced activity may result in increased susceptibility of affected cells to oxidative stress. Other implicated pathways that may contribute to the pathogenesis of HD include altered expression of the growth factor brain-derived neurotrophic factor (BDNF), and deleterious effects of protein aggregates, which may disrupt both proteasomal and autophagic degradation pathways.

MORPHOLOGY

The brain is small and shows striking **atrophy of the caudate nucleus** and, less markedly at early stages, the putamen (Fig. 28-42). The globus pallidus may atrophy secondarily, and the lateral and third ventricles are dilated. Atrophy is frequently also seen in the frontal lobe, less often in the parietal lobe, and occasionally throughout the entire cortex. On microscopic examination, there is profound loss of striatal neurons; the most marked changes are found in the caudate nucleus, especially in the tail and in portions nearer the ventricle. Pathologic changes develop in a medial-to-lateral direction in the caudate and from dorsal to ventral in the putamen. The nucleus accumbens is the best-preserved portion of the striatum. Both the large and small neurons are affected, but loss of the small neurons generally occurs first. The medium-sized, spiny neurons that use γ-aminobutyric acid as their neurotransmitter, along with enkephalin, dynorphin, and substance P, are especially affected. Two populations of neurons are relatively spared: the diaphorase-positive neurons that express nitric oxide synthase and the large cholinesterase-positive neurons. Both appear to serve as local interneurons. There is also fibrillary gliosis that is more extensive than in the usual reaction to neuronal loss. There is a direct relationship between the degree of degeneration in the striatum and the severity of clinical symptoms. Protein aggregates containing huntingtin can be found in neurons in the striatum and cerebral cortex (Fig. 28-42, *inset*).

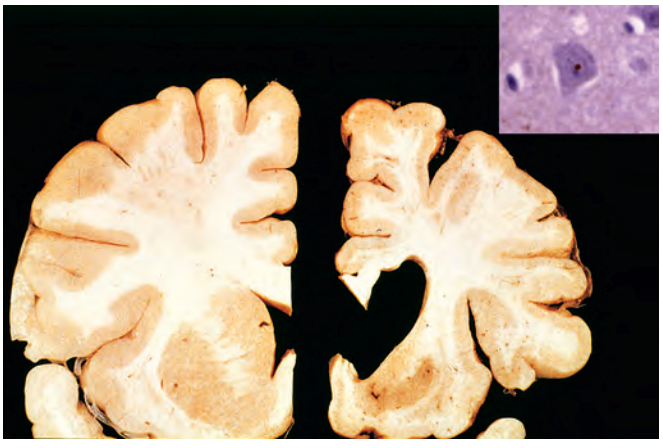

Figure 28-42 Huntington disease. Normal hemisphere on the left compared with the hemisphere with Huntington disease on the right showing atrophy of the striatum and ventricular dilation. *Inset*, Intranuclear inclusions in neurons are highlighted by immunohistochemistry against ubiquitin. (Courtesy Dr. J-P Vonsattel, Columbia University, New York.)

Clinical Features. The loss of medium spiny striatal neurons leads to dysregulation of the basal ganglia circuitry that modulates motor output. These neurons normally function to dampen motor activity; thus, their degeneration in HD results in increased motor output, often manifested as choreoathetosis. The cognitive changes associated with the disease are probably related to the neuronal loss from cerebral cortex.

The age at onset is most commonly in the fourth and fifth decades and is related to the length of the CAG repeat in the *HTT* gene. Motor symptoms often precede the cognitive impairment. The movement disorder of HD is choreiform, with increased and involuntary jerky movements of all parts of the body; writhing movements of the extremities are typical. Early symptoms of higher cortical dysfunction include forgetfulness and thought and affective disorders, but there is progression to a severe dementia. Although individuals with HD have an increased risk of suicide, intercurrent infection is the most common natural cause of death. Given the ability to screen for disease-causing mutations, one might assume that genetic screening of individuals at risk would be routine. However, this is an example of a situation where the ability to detect the likelihood of disease has surpassed any possible treatment. Thus, in the absence of effective therapy and given the devastating nature of the disease, it is not entirely clear that screening is ethical.

Spinocerebellar Degenerations

These degenerative diseases involve the cerebellum along with other components of the nervous system, commonly the spinal cord (both tracts that project to the cerebellum as well as the dorsal columns, which do not) and peripheral nerve. Because of the anatomic location of the lesions, clinical symptoms commonly include cerebellar and sensory ataxia, spasticity, and sensorimotor peripheral neuropathy. Despite the overlap in regions of involvement, this is a highly heterogeneous group of illnesses at the clinical, genetic and pathologic level, with differences in patterns of inheritance, age at onset, and signs and symptoms. What is common across them is the presence of neuronal loss, often without other distinctive changes apart from gliosis, in the affected areas. Genetic analysis continues to change our classification of these illnesses, but frustratingly this has yet to lead to clearer insight into their pathogenesis or to effective treatments.

The term *spinocerebellar ataxia* (SCA) is usually applied to a series of autosomal dominantly inherited disorders. We will also briefly discuss two of the more common autosomal recessive disorders that are characterized by spinocerebellar degeneration, Friedreich ataxia and ataxia-telangiectasia. Finally, there is a small set of hereditary disorders characterized by episodes of ataxia or other symptoms of cerebellar dysfunction, which are mostly associated with mutations in genes for ion channel subunits.

Spinocerebellar Ataxias

This group of genetic disorders presents with signs and symptoms referable to the cerebellum (progressive ataxia), brainstem, spinal cord, and peripheral nerves, as well as other brain regions in different subtypes.